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Title

Evolution of cumulative live birth, cumulative multiple live birth and drop-out rates over six complete IVF/ICSI cycles: a large prospective cohort study.

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Abstract

Research question: How do cumulative live birth rates (CLBR), cumulative multiple live birth rates (CMLBR) and drop-out rates over six complete IVF/ICSI cycles change over time?

Design: A prospective longitudinal cohort of 16 073 patients who started a first fresh ART cycle between January 1, 2014 until December 31, 2016 with follow up until December 31, 2017 included 48 946 cycles. Comparison of outcomes between the current (2014-2017) and a previous period (2009-2012) was performed.

Results: The conservative estimates of CLBR after six complete cycles were significantly higher in women <35 years of age after every cycle and after the first cycle in women of 35-37 years old in the period 2014-2017 compared to 2009-2012. For the optimal estimate, the CLBR was significantly higher after the first three cycles in women <35 years and after the first cycle in women 35-37 years of age when the two periods were compared.

CMLBR rate showed a further decline to 4.1% ±0.16 (SE) for the conservative estimate and 6.7% ± 0.30 (SE) for the optimal estimate after 6 complete cycles for the whole cohort.

Drop-out rates of complete cycles were as high as 26.5% 29.4%, 33.4 %, 38.9% and 47.3% after the first, second, third, fourth and fifth cycle, respectively. Compared to 2009-2012, the drop-out rate in the current period was significantly higher for cycle 1 ($p<0.0001$) and cycle 2 ($p= 0.0124$).

Conclusion: CLBR and drop-out rates over six complete IVF/ICSI cycles increase and MLBR shows a further decline when 2014-2017 was compared to 2009-2012.

Key message:

Cumulative live birth rates over six complete IVF/ICSI cycles increase and cumulative multiple live birth rates further decrease when 2014-2017 was compared to 2009-2012. However drop-out rates remain high and increase after cycle 1 and 2 and this warrants further attention.

Key words: cumulative live birth rate, drop-out rate, discontinuation, IVF/ICSI

Introduction

Although there is still a lot of debate on the best outcome parameter to show and compare outcome and safety in terms of pregnancies with multiple gestation after ART, it is agreed by many authors that effectiveness and safety should be reported separately (Braakhekke et al., 2015 and Wilkinson et al., 2017), rather than reporting the cumulative live birth of a healthy singleton (Barnhart., 2014). To fully inform the patients on the chances of success of an ART treatment, calculations need to be done on the patient's level rather than on the cycle level. The cumulative live birth rate (CLBR) accurately reflects the effectiveness of ART and takes into account patients who discontinue their treatment (De Neubourg et al., 2016) as well as recent advances in cryopreservation technology with an increasing number of freeze all cycles for different reasons (Blockeel et al, 2019). Safety issues of ART are reflected in cumulative multiple live birth rate.

Calculating CLBRs remains a challenge compared to presenting data as live birth rate per cycle, the latter being an easy way of presenting outcome, provided the denominator is clearly defined (Wilkinson et al., 2016). We previously analyzed CLBRs in the period from 2009-2012 to investigate whether the reduction in the number of pregnancies with multiple gestation was at the expense of success for the patients. It appeared that this was not the case at all when CLBRs were compared to other registries and studies that showed similar low multiple gestation/live births (De Neubourg et al., 2016). However, some additional factors that could challenge comparisons of CLBRs were highlighted. Indeed, when analysing CLBRs, high drop-out rates of 23.7% after the first complete cycle increasing to 27.3%, 33%, 40.8% and 46.9% % after the second to fifth complete cycles for all women <43 years of age were detected (De Neubourg et al., 2016). This is an important finding in a health care system where ninety percent of the IVF/ICSI cycle related costs are covered and where drop-out rates could be calculated because the national registry enables to track the patient even if she changes between ART centres.

A new initiative was taken to evaluate whether there was any evolution in CLBRs and drop-out rates including some parameters that may influence outcomes such as the woman's age and the number of cycles between two periods, i.e. 2014-2017 and 2009-2012, when using the same methodology.

Materials and methods

Study population and data collection system

All patients <43 years of age with a Belgian national insurance number who started a first fresh ART cycle between January 1, 2014 until December 31, 2016 with follow up until December 31, 2017 were included in the analysis. Registration of all ART cycles by the centres is mandatory in Belgium (De Neubourg et al., 2013) and consent for transmitting non-identifying data is signed by the patients in the respective fertility centres. The data are communicated and stored in the National register. A unique identification number is generated by the system at the start of the IVF/ICSI or frozen-thawed cycle and allows data collection in a prospective manner of each specific cycle. The addition of a hashed version of the patients' Belgian national insurance number to a cycle makes it possible to collect every treatment cycle of a patient. After data quality check and after resolving data inconsistencies, data are analysed. The registration system allows follow-up of all subsequent cycles from a patient even when she changes from one centre to another.

Only autologous cycles were studied. For the division in age categories, the patient was allocated to the age category at the time of her first cycle. CLBRs were calculated per fresh non-cancelled cycle with all frozen-thawed embryo transfer cycles attached to the fresh cycle of origin (complete cycle). A consecutive use of cryopreserved embryos is obligatory before new embryos may be created in Belgium (De Neubourg et al., 2013). Up to six fresh cycles for a maximum duration of 48 months since the start of the first oocyte retrieval were analysed.

Patients were excluded from the analysis if they had no Belgian insurance number, if the women had a prior IVF/ICSI cycle (both fresh and frozen-thawed embryo transfer cycle), underwent pre-implantation genetic testing (PGT) or in vitro maturation (IVM). Cycles after the first live birth after a previous ART cycle, cycles with the use of donor oocytes or fresh cycles with a higher rank than six were also excluded.

Outcome parameters

Live birth was defined as the live birth of a baby ≥500g or ≥22 weeks of gestation if birth weight was unknown (Zegers-Hochchild et al., 2017). Deliveries of a pregnancy with multiple gestation are counted as one live birth. Cycles for which the live birth status was unknown due to the fact that the patient was lost-to-follow up were imputed as follows: cycles in which fetuses were still observed on a 20 to 25 week ultrasound scan were assumed to have led to a live birth, other cycles were assumed not to have led to a live birth.

Statistical methods

Conservative estimates of the CLBR assumed that women who did not return for treatment would not have a live birth and thus ~~potentially~~ underestimates CLBR whereas optimal estimates of CLBR assumed that these women would have live birth rates similar to those for women continuing treatment and create on overestimate. The conservative estimate of CLBR was calculated as the number of live births up to and including a specific cycle, divided by the number of women who started their first ART cycle during the study period. The optimal estimate of CLBR was based on the Kaplan–Meier estimate when all cycles were included in the analysis. The standard errors (SE) for both these live birth rates were computed with the use of the binomial distribution. Differences in CLBR between age groups were assessed with the use of the log-rank test. The analysis for cumulative multiple live births is done similarly with a multiple live birth as event.

The conditional live birth rate at a specific cycle was the probability of a live birth at that cycle and was equal to the number of live births per course of treatment divided by the number of women who received ART treatment at that cycle.

The drop-out rate of a complete cycle was calculated as the number of patients who did not have a live birth and did not proceed to a next fresh cycle divided by the number of women who did not have a live birth. Drop-out rates were compared between periods or age categories by means of a Chi-square test. For all pair-wise comparisons between age categories, a Bonferroni correction for multiple testing was applied. All analyses were performed with SAS software, version 9.4. *No ethics approval was required for this research question (EC/PM/NVD/2020.077).*

Results

Characteristics of the study population and treatment cycles

The final data set for analysis included 16 073 patients and 48 946 cycles (both fresh and frozen cycles) (Figure1).

Age distribution was as follows: there were 10 055 patients <35 years of age; 2 620 aged between 35 and <38; 2 186 aged between 38 and <41 and 1 212 aged between 41 and <43. The mean age of the patients was 32.8 ± 5.07 (Standard deviation (SD)) in 2014-2017 compared to 32.2± 5.12 (SD) years ($p<0.0001$) in the previous period examined.

The mean number of fresh cycles per patient until live birth was 1.67 ±1.03 (SD) and significantly lower ($p<0.0001$) compared to 1.79 ± 1.09 (SD) for the 2009-2012 period. The number of cryo cycles per patient until live birth was 0.71 and significantly lower ($p<0.0001$) compared to 0.55 for the 2009-2012 period. Among all patients observed during the treatment period, 90.5% (of patients) had their ART treatments in the same fertility centre, whereas 9.2% consulted two centres and 0.4% three or four centres. Selective embryo reduction was performed in 57 cycles (=0.2% of the fresh cycles). Before the censoring of cycles after live birth, pregnancy outcome per cycle was missing in 2.8% of the 52 694 cycles. All except four of those cycles did also not have data on pregnancy evolution at 20 to 25 weeks of gestation. They were presumed not to have had a live birth in the calculation of live birth estimates. The four cycles that did have data on pregnancy evolution at 20 to 25 weeks of gestation were imputed as having had a live birth.

Cumulative live birth rates

Table 1 gives an overview of the calculation of the conditional live birth rate, the conservative and optimal estimate of CLBR for the whole cohort up to six complete cycles. The conservative estimate of CLBR for all ages after 3 and 6 cycles is 51.6 ±0.39 (SE) and 55.4±0.39 (SE) respectively, whereas this is 61.2±0.46 (SE) and 76.8±0.64 (SE) for the optimistic estimate of CLBR. The conditional live birth rate declines from 33.2% to 14.1% over 6 cycles.

The conservative (Figure 2) and optimal (Figure 3) estimates of CLBR after six complete cycles per age category show a decrease with increasing age for both conservative and optimal estimates.

The conservative estimates of CLBR after six complete cycles are significantly higher in women <35 years of age after every cycle in period 2014-2017 compared to 2009-2012 and after the first cycle in women of 35-37 years. In the optimal estimate, the CLBR was significantly higher after the first three cycles in women <35 years and after the first cycle in women 35-37 years of age when the period 2014-2017 was compared to 2009-2012.

Cumulative multiple live birth rates

Overall, the cumulative multiple live birth rate was 4.1% ±0.16 (SE) for the conservative estimate and 6.7% ± 0.30 (SE) for the optimal estimate after 6 complete cycles for the whole cohort. In patients <35 years of age, a further decline in the cumulative multiple birth rate from 6.0% to 4.6% after six cycles was observed in the conservative estimate (Figure 4) and from 10.3% to 7.8% in the optimal estimate (Figure 5). In the latter approach the decrease is statistically significant from the third cycle onwards.

Drop-out rates

Drop-out rates of complete cycles were as high as 26.5% for patients who did not achieve a live birth after the first complete fresh cycle and increased to 29.4%, 33.4 %, 38.9% and 47.3% after the second to the fifth cycle, respectively. Drop-out rates calculated in a cumulative way showed that 52.6% of the patients who did not have a live birth had stopped further ART treatment after the second cycle and this was 72.3% after the third, 85.2% after the fourth and 93.3% after the fifth cycle, respectively. When compared to the period 2009-2012, the drop-out rate in the current period was significantly higher for cycle 1 ($p<0.0001$) and cycle 2 ($p= 0.0124$) but not for cycle 3 ($p= 0.6850$).

With regard to age, the drop-out rate for the 41-42 year age group was significantly higher after the first and second cycle compared to all age groups (38-40 year ($p=0.0005$), 35-37 year ($p=0.0394$) and <35 year (p-0.0063) after the first cycle and 38-40 year ($p<0.0001$), 36-37 year ($p<0.0001$), and <35 year ($p<0.0001$) after the second cycle respectively). After the third cycle, the drop-out rate for the 41-42 year age group was significantly higher than for the 38-40 year ($p=0.0004$) and 35-37 year ($p=0.0384$) age groups. After the fourth cycle, no significant difference between the age categories was found. The <35 year age group had significantly more drop-outs than the 38-40 year age group ($p=0.0049$) after the fifth cycle.

Discussion

While there was an increase of the mean age of the patient who started her first IVF/ICSI by a half year from 32.2 to 32.8 years of age during the period 2014-2017 (versus 2009-2012), we observed a significant decrease in the mean number of IVF/ICSI cycles until live birth ~~or drop-out~~ from 1.79 to 1.67 cycles. . This is probably due to a significant increase of the mean number of cryo cycles per patient until live birth from 0.55 for the 2009-2012 period to 0.71 for the 2014-2017 period.

In addition, our analysis shows that the CLBR after six complete cycles was significantly higher in women <35 years of age after every cycle in 2014-2017 compared to 2009-2012 and after the first cycle in women 35-37 years in the conservative estimate whereas in the optimal estimate, the CLBR was significantly higher after the first three cycles in women <35 years and after the first cycle in women 35-37 years of age.

It is interesting and important to detect a significant increase in CLBR for the younger patient population but the descriptive analysis of CLBR does not provide exploratory information to gain insight. Reasons for this increase may be changes in treatment strategies such as, e.g., increase of freeze-all cycles or blastocyst transfers or improved laboratory techniques, but this is not possible to analyse as this may vary per cycle and per centre. However, the progressive implementation of the vitrification technique is likely to have influenced this tendency (Rienzi et al., 2017).

However, more than one quarter of the patients (26.4%) who do not have a live birth do not embark on a second cycle and this is 29.4% and 33.4% after the second and third cycle, respectively. This is significantly higher after the first and second cycle than in 2009-2012. The older age group (40-42 years of age) is more affected than the younger patients after the first and second cycle and this was also described by Troude et al (2014). These patients may have chosen to switch to oocyte donation.

Although doctors may presume that all drop-out patients go to other fertility centres, this was the case for only 9.5% of all our patients. This is much lower than the 34.8% reported by Domar et al. (2018) who conducted a cross-sectional study in a private infertility centre where only one third of the patients discontinuing completed the survey. Whereas in many settings the expense of IVF treatment is an important reason for discontinuation (Bedrick et al., 2019), we may presume that this is not the case for most of the patients in our analysis. Indeed, for all of them 90% of the IVF/ICSI costs were covered. However, cost is likely not the only factor involved as it was previously observed in Sweden that 65% of couples not achieving a live birth interrupted the full treatment program of three cycles (Olivius et al., 2002).

We have to take into account that there is no exact manner to count drop-out of patients who have no live birth when calculating cumulative live birth rates and this is because the reason for drop-out is mostly unknown. Patients can refrain from further treatment because of informative censoring by the doctor on poor prognosis and/or because of the psychological burden of pursuing treatment. They may also experience serious relational problems or get pregnant spontaneously. Therefore, authors have suggested different manners of presenting discontinuation in ART. It was suggested by Gameiro et al. (2013) to talk about compliance with ART and take into account discontinuation as well as doctor censoring. When CLBR is calculated in a conservative approach, it will be underestimated in the younger patient population by giving them a zero chance of achieving a live birth in the next cycle and it will be overestimated in the optimal approach for older patients because their chance of having a successful next cycle will be lower than the one from the population still in treatment. This was confirmed by Modest et al (2018) who calculated CLBR using 'inverse probability weighting' by creating subpopulations of drop-outs that had similar characteristics to the patients still in treatment.

Another interesting observation is the further decline in the cumulative multiple birth rate in the younger patients <35 years with a statistically significant decrease from the third cycle onwards in the optimal estimate. This is an important finding because in this age category, mandatory single embryo transfer exists in the first two cycles only but it is clear that the field is now implying single embryo transfer more and more on a voluntary basis.

The strength of our study lies in the consistency and reliability of the data in a mandatory online registration system, allowing comparisons over time and being able to follow patients even when changing between fertility centers. The study covers the entire Belgian population where the social security system covers 99% of inhabitants and women have an easy access to fertility diagnosis and treatment. When indicated, women are allowed to have 6 complete IVF/ICSI cycles in their lifetime with a coverage of 90% of the costs until the age of 43 years. This coverage of the majority of costs is coupled to a restriction of the number of embryos transferred in relation to the age of the patient, rank of the cycle and embryo quality with the aim of reducing the number of pregnancies of multiple gestation. IVF/ICSI can only be performed in fertility clinics licensed by the government as banks for human reproductive tissues and cells. The results of our study will certainly apply for states or countries with a similar organization of the healthcare system.

The lack of information on the occurrence of spontaneous pregnancies could be seen as a limitation of the study. These pregnancies may add up to 17% treatment independent live births after previous

failed IVF/ICSI in a follow up period of 5 years (ElMokhallalati, 2019). Domar et al (2018) reported 24.1% spontaneous conceptions as a reason for discontinuation for at least one year among the women that completed the survey. One has to take into account that both studies represent a small cohort and that the study by Domar may present an overestimation of the good news of a spontaneous conception.

After tackling the most important complication of IVF/ICSI, which has been the high proportion of pregnancies with multiple gestation, the challenge for the future is to decrease the drop-out rates in which patients, often with a good prognosis to become pregnant with IVF/ICSI, discontinue the treatment. Reasons for drop out of patients can be related to patient characteristics, different aspects of the treatment and cycle as well as characteristics of the IVF clinic with a plea for more patient centered care (Gameiro 2012). Because of the burden of the treatment, all initiatives to support patients throughout the IVF journey are warmly welcomed and likely to make a bigger difference than losing themselves in discussion over small benefits of add-ons (Harper et al., 2017). It will be a challenge for both the health care providers in the fertility centers as well as the society at large to support these young patients and facilitate them to undergo and be able to continue their treatment.

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Declaration of interest:

DDN, CW have no conflict of interest pertaining to the content of the paper ; KB, EA , NG, CA, TC, FVDK have no conflict of interest to declare; CB has received unrestricted grants or lecture fees from Abbott, MSD, Merck, Gedeon-Richter, IBSA and Ferring Pharmaceuticals (but not related to the work under consideration); AD received unrestricted grants or lecture fees from Merck, Gedeon-Richter, and Ferring Pharmaceuticals but not related to the work under consideration.

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Legends to the figures:

Figure 1: IVF/ICSI cycles available for study before and after exclusions

Figure 2: Conservative estimate of cumulative live birth rate in 2009-2012 and 2014-2017.

Figure 3: Optimal estimate of cumulative live birth rate in 2009-2012 and 2014-2017.

Figure 4: Conservative estimate of cumulative multiple live birth rate in 2009-2012 and 2014-2017.

Figure 5: Optimal estimate of cumulative multiple live birth rate in 2009-2012 and 2014-2017.

Table 1: Calculation of the conditional live birth rate, the conservative and optimal estimate of CLBR for the whole cohort up to six complete cycles (2014-2017)

Rank	Number of women	Number of live births	Conditional live birth rate (%)	Conservative cumulative live birth rate (%)	Standard Error conservative cumulative live birth rate (%)	Optimal cumulative live birth rate (%)	Standard Error optimal cumulative live birth rate (%)	Withdrawal (%)
1	16073	5336	33.2	33.2	0.37	33.2	0.37	.
2	7891	2092	26.5	46.2	0.39	50.9	0.43	26.5
3	4096	862	21.0	51.6	0.39	61.2	0.46	29.4
4	2155	359	16.7	53.8	0.39	67.7	0.49	33.4
5	1097	180	16.4	54.9	0.39	73.0	0.55	38.9
6	483	68	14.1	55.4	0.39	76.8	0.64	47.3

Figure 1

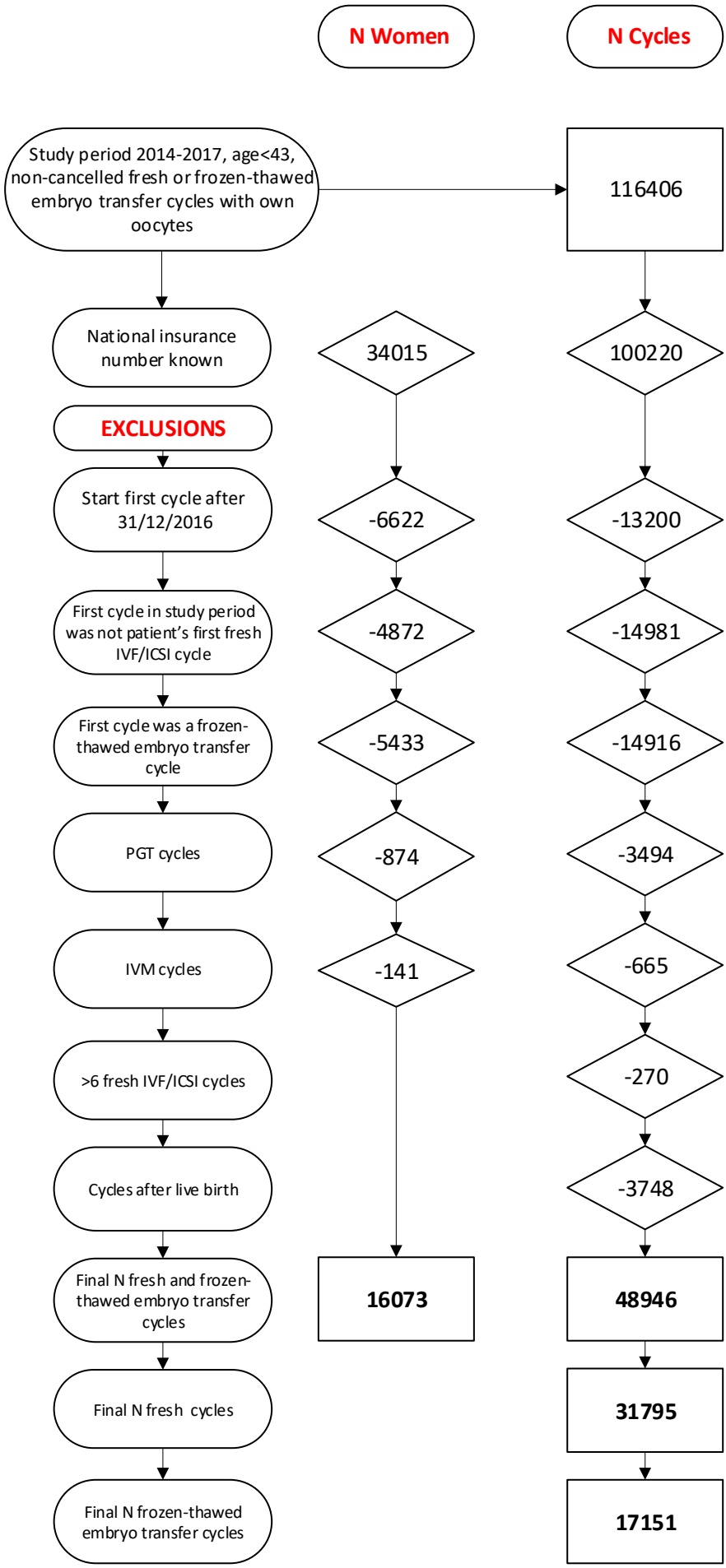

N Women
N Cycles
Study period 2014-2017, age<43, non-cancelled fresh or frozen-thawed embryo transfer cycles with own oocytes
116406
National insurance number known
34015
100220
EXCLUSIONS
Start first cycle after 31/12/2016
-6622
-13200
First cycle in study period was not patient's first fresh IVF/ICSI cycle
-4872
-14981
First cycle was a frozen-thawed embryo transfer cycle
-5433
-14916
PGT cycles
-874
-3494
IVM cycles
-141
-665
>6 fresh IVF/ICSI cycles
-270
Cycles after live birth
-3748
Final N fresh and frozen-thawed embryo transfer cycles
16073
48946
Final N fresh cycles
31795
Final N frozen-thawed embryo transfer cycles
17151

Figure 2

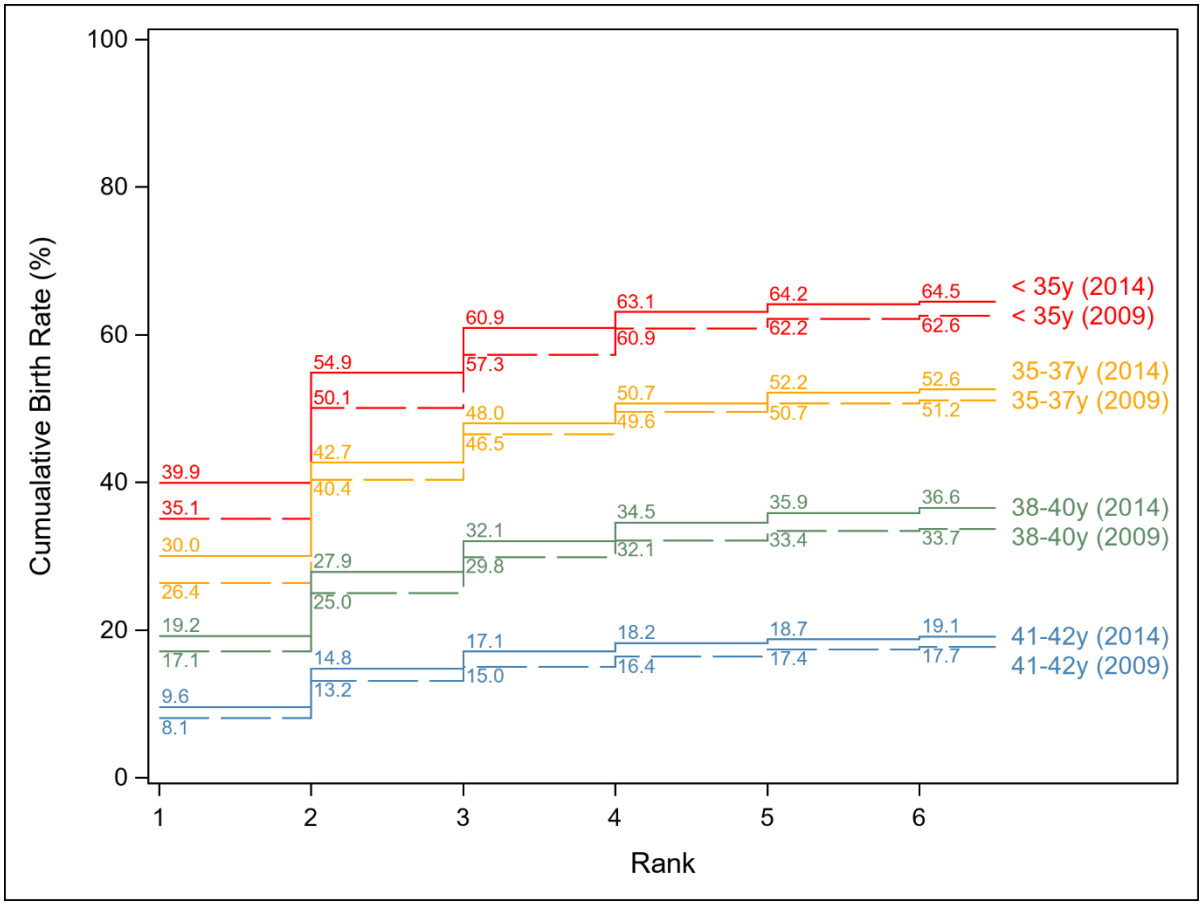

Cumulative Birth Rate (%)
100
80
60
40
20
0
1
2
3
4
5
6
Rank
39.9
35.1
30.0
26.4
19.2
17.1
9.6
8.1
54.9
50.1
42.7
40.4
27.9
25.0
14.8
13.2
60.9
57.3
48.0
46.5
32.1
29.8
17.1
15.0
63.1
60.9
50.7
49.6
34.5
32.1
18.2
16.4
64.2
62.2
52.2
50.7
35.9
33.4
18.7
17.4
64.5
62.6
52.6
51.2
36.6
33.7
19.1
17.7
< 35y (2014)
< 35y (2009)
35-37y (2014)
35-37y (2009)
38-40y (2014)
38-40y (2009)
41-42y (2014)
41-42y (2009)

Figure 3

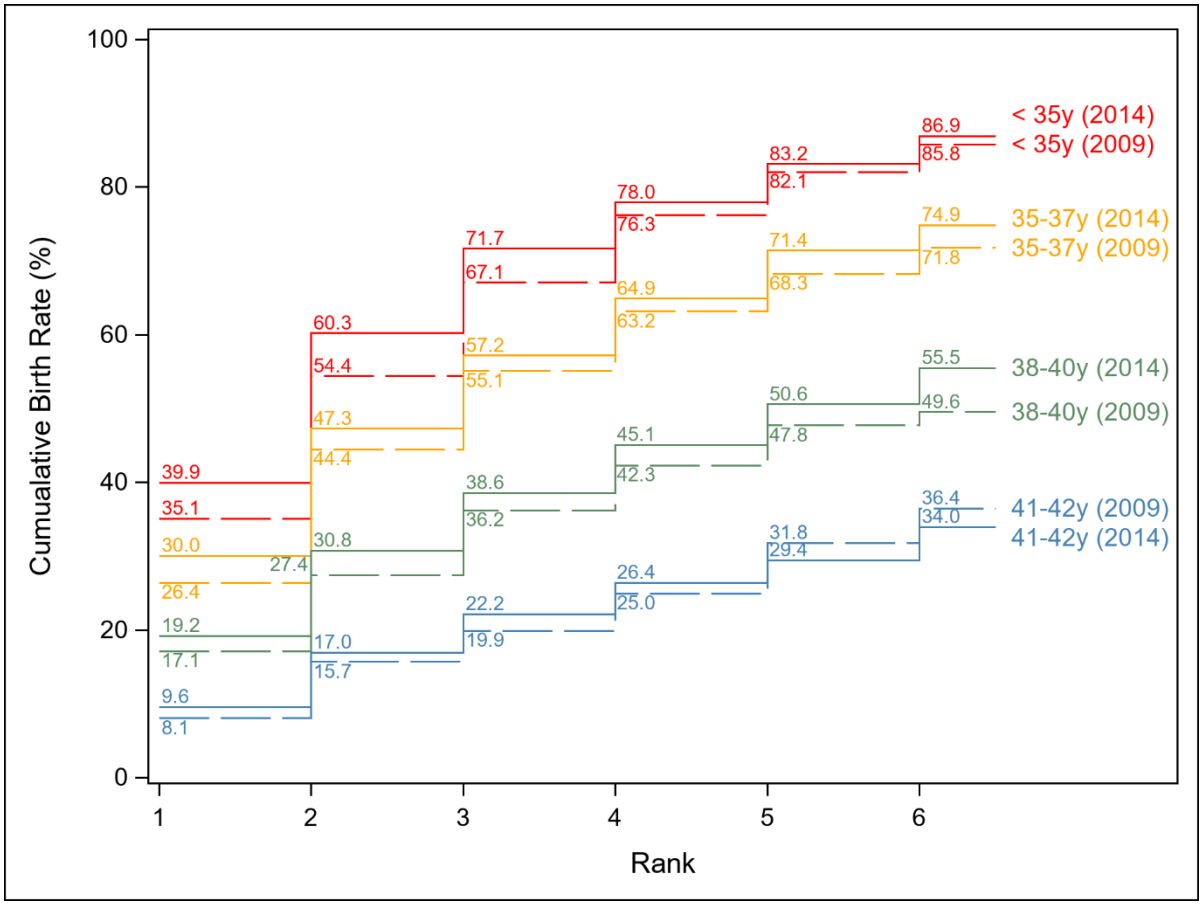

Cumulative Birth Rate (%)
100
80
60
40
20
0
1
2
3
4
5
6
Rank
< 35y (2014)
< 35y (2009)
35-37y (2014)
35-37y (2009)
38-40y (2014)
38-40y (2009)
41-42y (2009)
41-42y (2014)
39.9
35.1
60.3
54.4
71.7
67.1
78.0
76.3
83.2
82.1
86.9
85.8
30.0
26.4
47.3
44.4
57.2
55.1
64.9
63.2
71.4
68.3
74.9
71.8
19.2
17.1
30.8
27.4
38.6
36.2
45.1
42.3
50.6
47.8
55.5
49.6
9.6
8.1
17.0
15.7
22.2
19.9
26.4
25.0
31.8
29.4
36.4
34.0

Figure 4

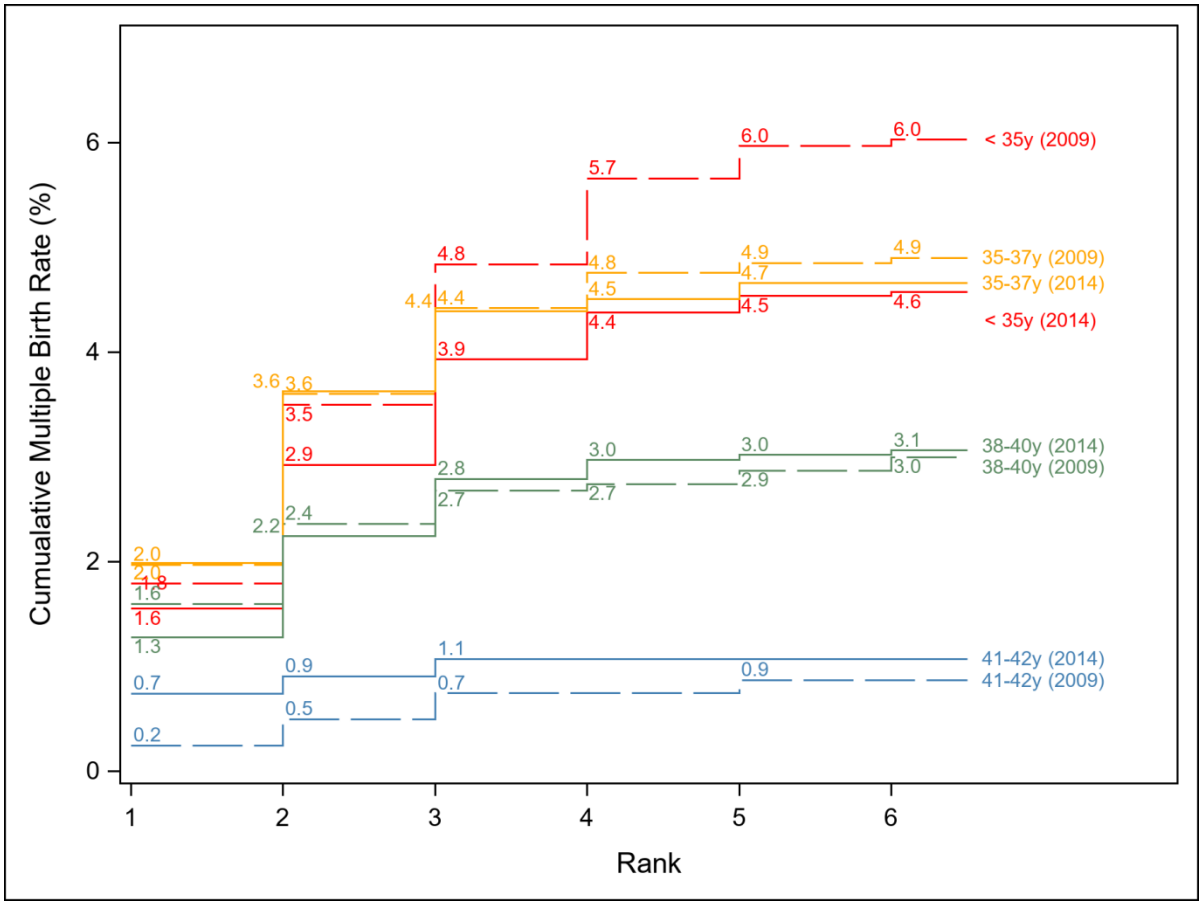
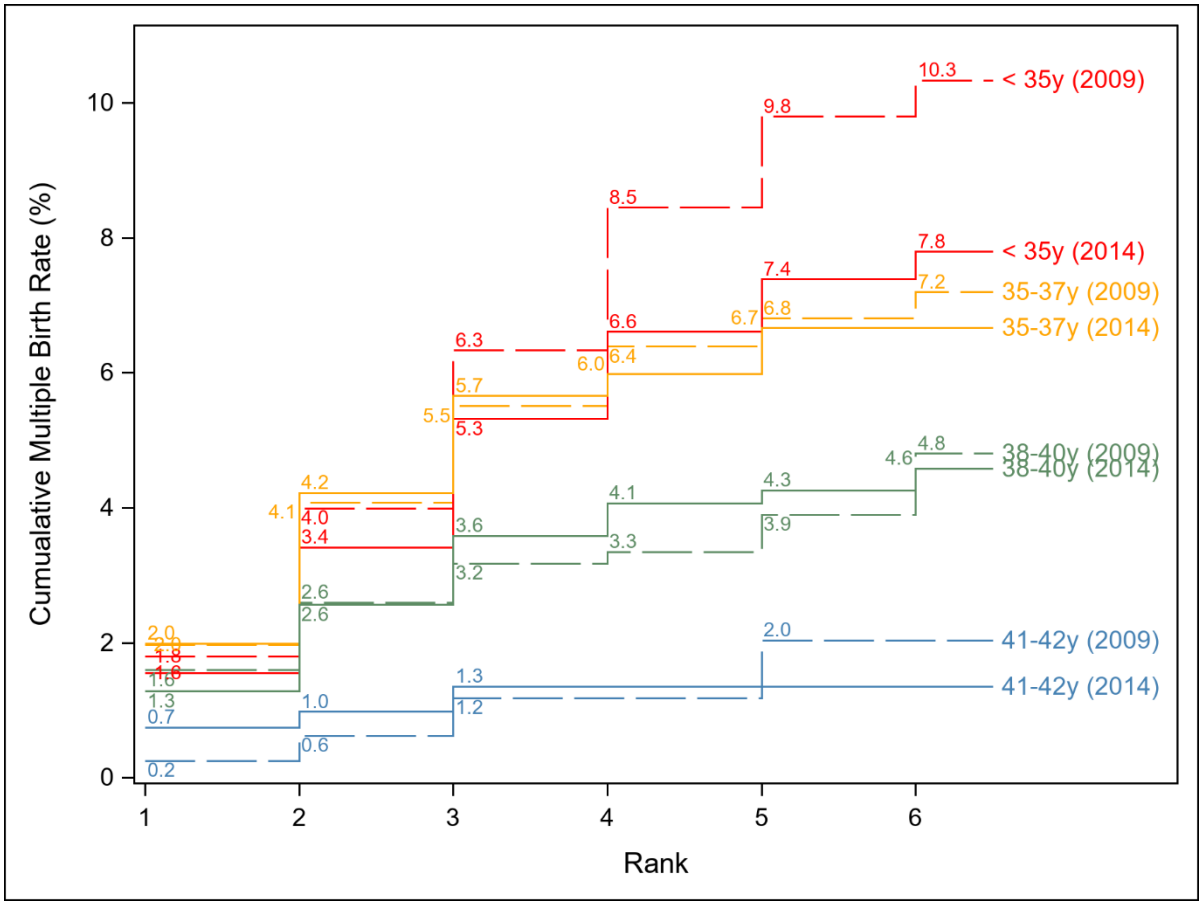

Cumulative Multiple Birth Rate (%)
0
2
4
6
1
2
3
4
5
6
Rank
< 35y (2009)
35-37y (2009)
35-37y (2014)
< 35y (2014)
38-40y (2014)
38-40y (2009)
41-42y (2014)
41-42y (2009)

Figure 5


Cumulative Multiple Birth Rate (%)
Rank
< 35y (2009)
< 35y (2014)
35-37y (2009)
35-37y (2014)
38-40y (2009)
38-40y (2014)
41-42y (2009)
41-42y (2014)